Stage-specific Effects of Bioactive Lipids on Human iPSC Cardiac Differentiation and Cardiomyocyte Proliferation.

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Public Summary:
Bioactive lipids such as sphingosine-1-phosphate (S1P) and lysophosphatidic acid (LPA) regulate diverse processes including cell proliferation, differentiation, and migration. However, their roles in cardiac differentiation and cardiomyocyte proliferation have not been explored. Using a 96-well differentiation platform for generating human induced pluripotent stem cell-derived cardiomyocytes (hiPSC-CMs) we found that S1P and LPA can independently enhance cardiomyocyte generation when administered at an early stage of differentiation. We showed that the combined S1P and LPA treatment of undifferentiated hiPSCs resulted in increased nuclear accumulation of β-catenin, the canonical Wnt signaling pathway mediator, and synergized with CHIR99021, a glycogen synthase kinase 3 beta inhibitor, to enhance mesodermal induction and subsequent cardiac differentiation. At later stages of cardiac differentiation, the addition of S1P and LPA resulted in cell cycle initiation in hiPSC-CMs, an effect mediated through increased ERK signaling. Although the addition of S1P and LPA alone was insufficient to induce cell division, it was able to enhance β-catenin-mediated hiPSC-CM proliferation. In summary, we demonstrated a developmental stage-specific effect of bioactive lipids to enhance hiPSC-CM differentiation and proliferation via modulating the effect of canonical Wnt/β-catenin and ERK signaling. These findings may improve hiPSC-CM generation for cardiac disease modeling, precision medicine, and regenerative therapies.

Scientific Abstract:
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